

Wilson disease with hepatic presentation in an eight-month-old boy

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Author contributions: Wang JS conceived the study, treated and followed up the index patient, revised the manuscript, and approved the submission of the final draft; Abuduxikuer K wrote the manuscript, retrieved relevant information from patient files, contacted the family for further information, determined the nature of genetic mutations by consulting genetic databases, and submitted the approved draft; Li LT, Qiu YL and Wang NL collected patient files, contributed to writing the manuscript, and conducted genetic analysis.

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Abstract

Wilson disease is an autosomal recessive disorder of copper metabolism that can cause fatal neurological and hepatic disease if not diagnosed and treated. The youngest child with normal liver function reported so far is an 8-mo-old Japanese boy with low ceruloplasmin levels, and the youngest child with elevated amino-transferase ever reported so far is a 9-mo-old Korean boy with confirmed by genetic testing. Here we report an 8-mo-old Chinese boy presented with elevated liver enzymes, and low serum ceruloplasmin level. Genetic analysis of *ATP7B* gene detected two heterozygous disease causing mutations (c.2621C>T/p.A874V and c.3809A>G/p.N1270S), and parental origins were determined. Persistent elevation of serum amino-transferase in this infant was normalized after zinc therapy. To our best knowledge, this is the youngest patient with elevated liver enzymes ever reported worldwide. We hope that this will raise awareness among pediatricians, leading to earlier diagnosis, timely treatment, and better clinical outcome.

Key words: Wilson disease; Infant; Hepatic presentation; *ATP7B*; Copper; Zinc

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Core tip: Wilson disease is rarely diagnosed during

infancy. The youngest child with normal liver function reported so far is an 8-mo-old Japanese boy, and the youngest child with liver function abnormality is a 9-mo-old Korean boy. Here we report an 8-mo-old Chinese boy presented with elevated liver enzymes, and low serum ceruloplasmin level. Diagnosis of Wilson disease was confirmed with *ATP7B* gene sequencing of the index case, and parental origins of disease causing mutations were outlined. To our best knowledge, this is the youngest patient with elevated liver enzymes ever reported worldwide.

Abuduxikuer K, Li LT, Qiu YL, Wang NL, Wang JS. Wilson disease with hepatic presentation in an eight-month-old boy. *World J Gastroenterol* 2015; 21(29): 8981-8984 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i29/8981.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i29.8981>

INTRODUCTION

Wilson disease (WD) is an autosomal recessive disorder of copper metabolism caused by *ATP7B* gene mutation. It can cause fatal damage to the liver and brain tissues if not diagnosed and treated earlier. Age at disease onset or appearance of clinical symptoms can vary markedly among patients^[1]. The youngest child with normal liver function reported so far is an 8-mo-old Japanese boy with a low ceruloplasmin level^[2]. In terms of liver function abnormality, the youngest child ever reported so far is a 9-mo-old Korean boy with elevated aminotransferase confirmed by genetic testing^[3]. Here we report an 8-mo-old Chinese boy who presented with elevated liver enzymes, and the diagnosis of WD was confirmed after *ATP7B* gene sequencing.

CASE REPORT

This boy first discovered to have abnormal liver function after routine blood testing during a diarrhea admission at 8-mo of age. After persistent elevation of serum alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels, WD was suspected. Serum ceruloplasmin level was found to be extremely low, and disease causing mutations were found on *ATP7B* gene sequencing. The patient was given oral zinc therapy with 10 mg of elemental zinc 3 times daily. At 14 mo of age, liver function significantly improved but ALT and AST levels were still above normal range. Persistent normalization was achieved after zinc gluconate dosage was increased to 20 mg/3-times-a-day (Table 1). Clinical examinations were negative for hepatomegaly, splenomegaly, K-F ring, and sunflower cataract. Other causes of serum aminotransferase elevation, such as viral hepatitis, muscle disorders, and hemolytic diseases were ruled out with proper investigations.

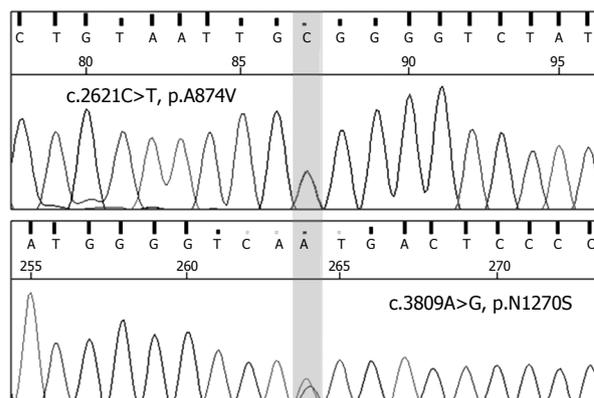


Figure 1 *ATP7B* gene sequencing detected two heterozygous mutations (p.A874V and p.N1270S) that have been reported to cause Wilson disease in the Wilson Disease Mutation Database (<http://www.wilsondisease.med.ualberta.ca/database.asp>), and predicted to be disease causing by Mutation Taster (<http://www.mutationtaster.org>).

The *ATP7B* gene sequencing detected two heterozygous mutations (p.A874V and p.N1270S) that have been reported to cause WD in the Wilson Disease Mutation Database (<http://www.wilsondisease.med.ualberta.ca/database.asp>), and predicted to be disease causing by MutationTaster (<http://www.mutationtaster.org>) (Figure 1). Sequencing also revealed 4 other heterozygous non-synonymous alleles and 1 allele in the non-coding region, mutationtaster predicted them to be single nucleotide polymorphisms (SNPs). Both parents were screened for disease causing mutations and the SNP in the non-coding region. Father was heterozygous for the mutation of c.3809A>G (p.N1270S), and mother was heterozygous for c.2621C>T (p.A874V), and c.3903+6C>T (Table 2).

At the age of 23 mo, the patient was slightly undernourished with a weight of 11.5 kg (below 50th percentile by The WHO Child Growth Standards: <http://www.who.int/childgrowth/standards/en/>) and a height of 83 cm (below 15th percentile). At the last follow-up when the patient was 35 mo of age, liver function test was normal. Linear growth had significantly improved with weight for age reaching above the 50th percentile (14.5 kg), and height for age reaching above the 15th percentile (93 cm).

DISCUSSION

Shimizu *et al*^[2] reported an 8-mo-old Japanese boy found to have low level of ceruloplasmin after mass screening. This child had normal liver function test results, and normal urinary copper excretion. However, the *ATP7B* gene sequencing detected a homozygous frame-shift mutation (c.2302insC). Kim *et al*^[3] reported a 9-mo-old male infant with elevated aminotransferase detected after routine blood testing for acute diarrhea. The serum ceruloplasmin level was below normal range, but the 24-h urinary copper excretion was normal. Compound heterozygous

Table 1 Biochemical test results and treatment at various stages

Age (mo)	ALT (Normal range 0-40 IU/L)	AST (Normal range 0-40 IU/L)	GGT (Normal range 7-50 IU/L)	TBA (Normal range 0-10 umol/L)	Ceruloplasmin (Normal range 0.21-0.53 g/L)	Treatment
8	247	193	ND	ND	ND	
10	270	104	75	47.5	ND	
11	350	185	ND	ND	0.079	zinc 30 mg/d
14	152	83	ND	ND	ND	zinc 60 mg/d
24	43	30	22	2.9	ND	zinc 60 mg/d
35	37	26	ND	ND	ND	zinc 60 mg/d

ALP: Alkaline phosphatase; ALT: Alaninaminotransferase; AST: Aspartate amino transferase; GGT: Gamma glutamyl transpeptidase; TBA: Total bile acid; ND: Not done.

Table 2 *ATP7B* gene sequencing results

Exons	Heterozygous mutation/allele (parental origin)	SNP number	Status on WD mutation database	Mutation taster prediction (score)
Exon2	c.1216T>G, p.S406A (ND)	rs1801243	Non disease causing	Polymorphism (99)
Exon3	c.1366G>C, p.V456L (ND)	rs1801244	Not found	Polymorphism (32)
Exon10	c.2495A>G, p.K832R (ND)	rs1061472	Non disease causing	Polymorphism (26)
Exon11	c.2621C>T, p.A874V (Mother)	rs121907994/CM980173	Disease causing	disease causing (64)
Exon12	c.2855G>A, p.R952K (ND)	rs732774	Not found	Polymorphism (26)
Exon16	c.3419T>C, p.V1140A (ND)	rs1801249	Not found	Polymorphism (64)
Exon18	c.3809A>G, p.N1270S (Father)	rs121907990/CM994116, CM930060	Disease causing	disease causing (46)
Intron	c.3903+6C>T (Mother)	rs2282057	Not found	Polymorphism

Wilson Disease Mutation Database (<http://www.wilsondisease.med.ualberta.ca/database.asp>); Mutation Taster (<http://www.mutationtaster.org>); ND: Parental sequencing not done.

mutations were found with genetic analysis (known disease causing mutation of p.G1186S, and novel frameshift mutation of c.4006delA that resulted a stop codon).

The reason why this patient had such an early disease onset could be genetic, environmental, or combination of both. Two known disease causing mutations were detected in this patient, along with 5 other non-synonymous SNPs plus 1 SNP in the non-coding region. Non-synonymous SNPs might not be disease causing when appeared alone, but it is unknown whether it can contribute to disease process when appeared in combination with other disease causing mutations, or with other non-synonymous SNPs. Over consumption of copper could be considered as one of the causes of early WD onset. An epidemiologic study of serum copper levels in 8 provinces of China revealed that serum copper levels in people from eastern China were significantly higher than that of middle and western China^[4]. Authors also conducted a survey proving that more frequent sea food consumption led to significantly higher copper levels in the body. Dietary and environmental factors may have played a role since coastal regions in eastern China are more industrialized, and people living there consumes more sea food than the people from other parts of the country. There is also evidence that long-term high copper intake in healthy men led to significantly higher copper retention in the body, and homeostatic regulation was not sufficient to maintain a normal copper absorption^[5]. Our patient

came from the coastal Shandong Province in eastern China, and potentially higher exposure to dietary and environmental copper, coupled with potentially severe disruption of copper homeostasis caused by *ATP7B* gene mutation plus SNPs may have led to enough copper accumulation, and caused liver damage at this young age. However, further studies need to be done in order to elucidate the complex interplay among genotype, phenotype, and environmental factors (such as diet and pollution).

In conclusion, an elevation of serum aminotransferase during infancy should always prompt pediatricians to exclude WD with genetic testing if other causes are negative.

COMMENTS

Case characteristics

An 8-mo-old Chinese boy presented with elevated liver enzymes.

Clinical diagnosis

Diagnosis of Wilson disease (WD) is made after a ceruloplasmin testing and *ATP7B* gene sequencing.

Differential diagnosis

Other causes of serum aminotransferase elevation, such as viral hepatitis, muscle disorders, and hemolytic diseases were ruled out with proper investigations.

Laboratory diagnosis

The serum ceruloplasmin level was extremely low, *ATP7B* gene sequencing revealed 2 disease causing mutations.

Imaging diagnosis

The liver and the gallbladder were normal on ultrasonography.

Treatment

Liver function improved and returned to normal after oral zinc gluconate therapy.

Related reports

The youngest WD child with normal liver function reported so far is an 8-mo-old Japanese boy, and the youngest child with elevated aminotransferase is a 9-mo-old Korean boy.

Experiences and lessons

An elevation of serum aminotransferase during infancy should always prompt pediatricians to exclude WD with genetic testing if other causes are negative.

Peer-review

Abuduxikuer *et al* have reported a case about an 8-mo-old Chinese boy that has been diagnosed with WD. The case report is interesting and factual.

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